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Identification of Risk Factors for Exertional Heat Illness: A Brief Commentary on Genetic Testing

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Objective: This commentary discusses known links between Exertional Heat Illness (EHI), Malignant Hyperthermia (MH), and other hereditary diseases of muscle. Genetic and functional testing is also evaluated as measures of fitness to return to duty/play. ***Data Sources***: Reviews and research articles from Sports Medicine, Applied Physiology, and Anesthesiology. ***Data Extraction***: Detailed comparisons of existing literature regarding clinical cases of EHI and MH and the potential utility of genetic testing, specifically the ryanodine receptor (RYR1) gene and other genes related to disorders of skeletal muscle. ***Data Synthesis*****:** EHI is a complex disorder wherein physiological, environmental, and hereditary factors interact to endanger an individual's ability to maintain thermal homeostasis. ***Conclusions***: Individuals' genetic background is likely to play an important role, particularly when EHI recurs. Recurrent EHI has been associated with MH and other genetic disorders, highlighting the importance of identification and exclusion of individuals with known high risk factors.

Exertional heat illness (EHI) is a complex disorder wherein physiological, environmental, and hereditary factors interact to endanger an individual's ability to maintain thermal homeostasis. Exertional heat stroke and heat exhaustion are two categories of EHI typically associated with exertional rhabdomyolysis. EHI may occur as an isolated event or recurrent episodes. Recurrence is sometimes seen in individuals with hereditary muscle disorders, including Malignant Hyperthermia (MH). Numerous articles have been published presenting cases of MH after strenuous exercise, excitement, and/or high environmental temperatures, suggesting that MH and EHI might be related syndromes.[1] The focus of this commentary concerns the otherwise healthy and acclimated war fighter/athlete who experiences an episode of EHI when others who are subjected to the same stressors do not. The goal should be identification and exclusion of individuals with known high risk factors for recurrence of EHI.

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EHI and MH

The link between EHI and MH, a subclinical myopathy, has been the subject of an ongoing debate for many years.[1-3] MH is an autosomal inherited disorder of calcium handling in skeletal muscle mainly due to mutations in the calcium release channel, type 1 ryanodine receptor (RYR1). The RYR1 belongs to a class of calcium ion channels located in the sarcoplasmic reticulum membrane that regulates release of calcium from intracellular stores. Until challenged by "triggering" inhalational anesthetics and/or succinylcholine, MH susceptible persons are asymptomatic and most are physically fit. Exposure to "triggering" anesthetic drugs can cause a life-threatening, hypermetabolic syndrome, known as a fulminant MH episode; similar (rare) events can be induced by high environmental temperatures, exertion, and/or stress, in the absence of anesthetic agents.[4-6] It is unknown what percentage of individuals with a history of EHI may be MH susceptible. Because MH is variably expressed, it is difficult to identify MH susceptible individuals before they (or a relative) have an episode. As such, war fighters/athletes may be susceptible to MH without knowing it. This presents a problem because they can be discharged as unfit for duty if found to be MH susceptible, even if they did not know this at the time of enlistment. The U.S. Department of Defense regulations identify MH as a disqualifying condition.

Definitive diagnosis of MH is made by a caffeine-halothane contracture test (CHCT) on a specimen of biopsied leg muscle. Muscle fibers from MH susceptible individuals are markedly more sensitive to RYR1 agonists halothane, caffeine, and 4-chloro-m-cresol. A reproducible left shift in the dose response curve of muscle contraction to these drugs has led to its use as the diagnostic indicator of MH. The sensitivity of CHCT is 97% (accurately identifies individuals with MH susceptibility), and the specificity is 78% (22% potential for a false positive result). The CHCT is invasive, expensive (approximately $5,000), and is not available in many areas of the country. These factors prevent testing of many persons who experience "suspicious" adverse responses to anesthesia, as well as EHI patients who might be referred for testing. Although molecular genetic analysis of the RyR1 is not yet a validated diagnostic test for MH susceptibility, it was incorporated as part of MH diagnostic testing in 2002.[7] Recent improvements in analysis show that sequencing the entire RyR1 has identified mutations considered causative for MH in up to 70% of cases, which shows potential for future diagnostic use.

EHI, MH, and Return to Duty/Play

Two issues require clarification before a recommendation can be made regarding the potential return to duty of those "well trained and acclimated war fighters/athletes who experience an episode of EHI." The first is whether these individuals are MH susceptible or not; the second is whether MH susceptible individuals are at greater risk for EHI than are the general population. To address the first issue of determining whether individuals are MH susceptible requires performing the validated diagnostic test for MH, the CHCT test (North America) or the in-vitro contracture test (IVCT: Europe). This test could be done either alone or in combination with RyR1 analysis. If either the CHCT or IVCT is positive, the diagnosis of MH susceptibility is given and the individual should be counseled about risk factors, to include anesthetic drugs, heat, and exertion. In addition, if a mutation in the RyR1 considered to be causative for MH in the CHCT-positive individual is identified, his/her relatives will benefit because they could be diagnosed as MH susceptible without a muscle biopsy if they have the same RyR1 mutation as their MH susceptible relative; however, a negative RyR1 genetic screen cannot rule out MH susceptibility.

The second question concerns the decades-old debate of whether or not MH susceptible individuals are at increased risk for EHI.[1-3] Although there are numerous reports of the association between EHI and MH at the clinical level, predisposition to EHI has only been shown definitively in one published case of MH.[5] A young male athlete who experienced heat stroke after vigorous participation in a game supports the position that MH susceptible individuals are at increased risk for EHI.[5] The athlete had experienced an anesthesia-induced clinical episode of MH during surgery eight months prior to the episode of heat stroke. At post mortem, a mutation considered causative for MH in the RyR1 was identified. Supporting the idea of a link between EHI and MH are numerous non-lethal cases of adverse responses to heat and physical exertion in MH susceptible individuals, some with RyR1 mutations, and also in many others in whom RyR1 analysis was not performed.[8]

Facing this reality, it is our recommendation that war fighters and athletes who have had an MH episode or who have a family history of MH (particularly a first-degree relative) be tested with the CHCT. War fighters and athletes with a history of recurrent EHI that cannot be explained by underlying metabolic or endocrine disorders should also be tested for MH susceptibility by CHCT and/or RyR1 genetic screen. Porter also, when writing about standards for the British military, advocates contracture testing.[9] Because of the high sensitivity of the CHCT, a negative CHCT result allows the individual to return to full duty. However, if the CHCT result is positive, the individual should not be assigned to duties that entail exposure to intense physical exertion and/or extreme heat. In these cases, the military has established protocols to "profile" such individuals and restrict exercise and work schedules to safe levels, as reviewed in O'Connor et al in this issue of the *Journal of Sport Rehabilitation*. Unfortunately, opportunities to retain war fighters who are heat intolerant for any reason have become limited, because the current requirement dictates that all soldiers must be world-wide deployable at any given time. All individuals who participate in highly competitive sports or enlist in the military should be queried about adverse reactions to anesthetics in their personal or family history, as well as prior heat-related illness. This would be an effective way of excluding some persons with a personal or family history of MH who may be unaware of the risks associated with potential MH susceptibility and physical exertion/heat.

EHI and Other Disorders

Other muscle characteristics/disorders have been associated with EHI. For instance, individuals with a high proportion of type II fibers have decreased work efficiency and are probably more susceptible to EHI. Hsu et al reported that patients with type II fiber predominance are more susceptible to exertional heat stroke and tend to have a higher blood lactate concentration and a shorter time to reach the blood lactate threshold under a treadmill load test.[10] Measurements of blood lactate threshold could be used as an indicator to monitor recovery following an EHI event and determine whether the individual is ready for full return to duty. In addition to screening the RyR1, analyzing a number of other genes associated with exertional stress events should be considered. Included are genes of energy metabolism, namely, carnitine palmitoyltranserase (CPT II) deficiency, myophosphorylase deficiency (McArdles disease), and myoadenylate deaminase (AMPD) deficiency. Other functional tests must also be considered. For example, the heat tolerance test where exercise is performed in a controlled environmental chamber has been shown to adequately discriminate between heat tolerant and intolerant individuals.[11,12] This would be an important area to investigate the interaction of environmental and genetic factors.

Conclusion

Our recommendations previously described expand the current protocol for identification and management of EHI, MH, and related muscle disorders that will allow for exclusion of at-risk individuals. The etiology of EHI and the relationship between MH and EHI are complex. We have yet to identify why some people under the exact same environmental circumstances develop EHI and others do not. Individual genetic mutations in the RyR1 and other genes (eg, metabolic myopathies) are likely to serve an important role, particularly when EHI is recurrent and/or there is a family predisposition to MH or other muscle disorders. Additional factors involved in muscle inflammation from exercise may also serve a role in both natural history and susceptibility to EHI. Clearly, environmental factors (diet, lifestyle, etc.) are important in the development of EHI.

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